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PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Manufacture of oct-3,5-dien-2,7-dione and oct-4-en-2,7-dione from oct-7-ol-3,5-dien-1-yne

We, EASTMAN KODAK COMPANY, a Company organized under the Laws of the State of New Jersey, United States of America, of 343, State Street, Rochester 4, New York, United States of America, (Assignees of CHARLES DONALD ROBESON and ALBERT JAMES CHECHAK) do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to the manufacture of oct-3,5-dien-2,7-dione and oct-4-en-2,7-dione from oct-7-ol-3,5-dien-1-yne, which may be prepared from sorbaldehyde via oct-4,6-dien-3-ol-1-yne.

According to the present invention there is provided a process for preparing Compound V which comprises oxidising Compound II to Compound III and then hydrating Compound III to form Compound V, or which comprises hydrating Compound II to form Compound IV and then oxidising Compound IV to Compound V, Compounds II, III, IV and V being defined hereinbelow.

As defined herein

Compound I is oct-4-6-dien-3-ol-1-yne
Compound II is oct-7-ol-3,5-dien-1-yne
Compound III is oct-7-one-3,5-dien-1-yne
Compound IV is oct-7-ol-3,5-dien-2-one and

Compound V is oct-3,5-dien-2,7-dione.

As used herein the term "oxidising" denotes the use of an oxidation method which results in the oxidation of the group $>CH.OH$ in Compound II or in Compound IV to the group $>C=O$, without affecting any of the unsaturated bonds in these compounds.

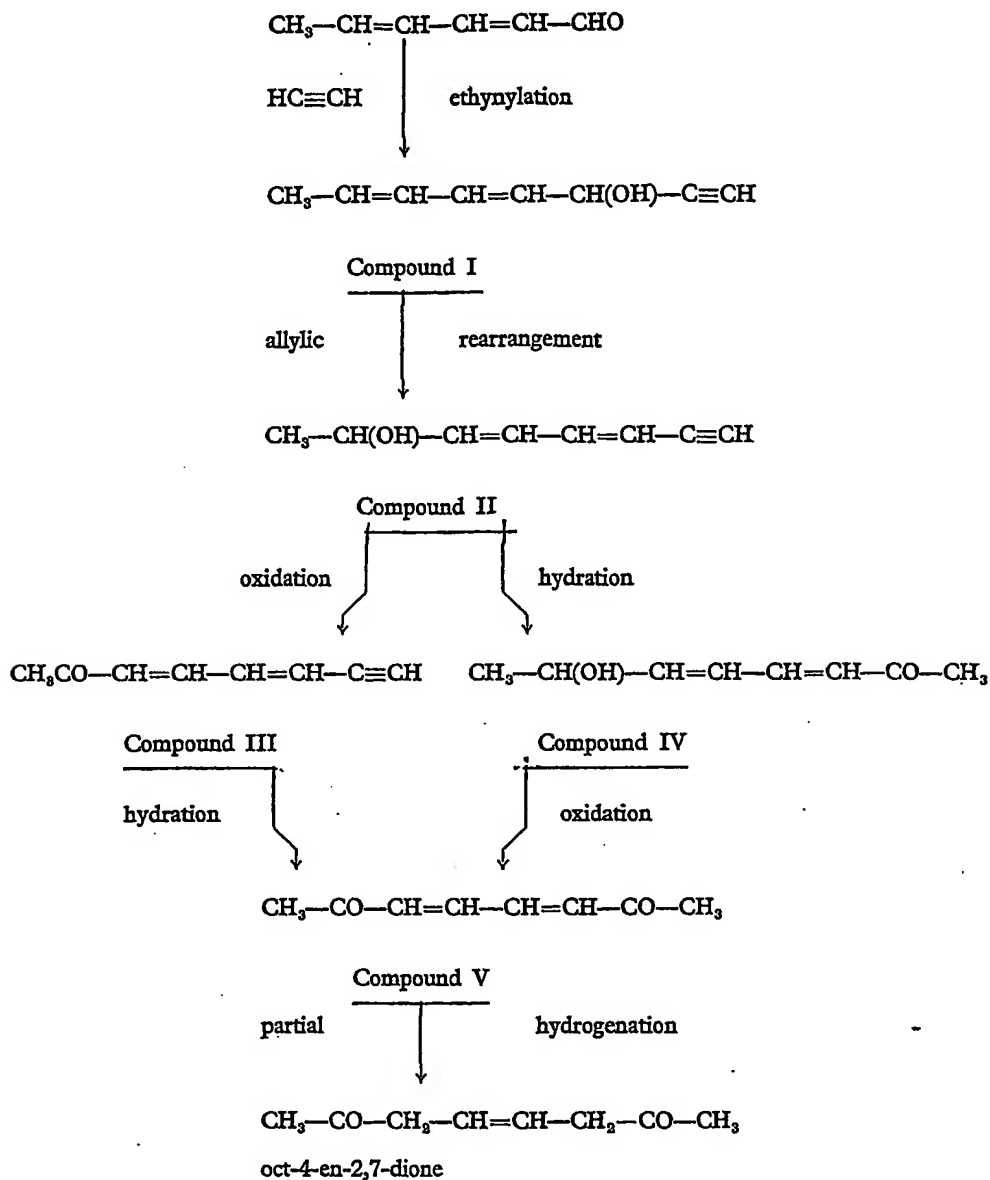
As used herein the term "hydrating" denotes the use of a hydration method which results in the addition of H_2O to the group $-C\equiv CH$ in Compound II or in Compound III to form the group $-CO-CH_2-$, without affecting any of the other unsaturated bonds in these compounds.

As used herein the term "ethynylation" denotes a preparative method which results in the addition of $-CH\equiv CH$ to the group $-CH=O$ in sorbaldehyde to form the group $-CH(OH)-C\equiv CH$.

As used herein the term "partially hydrogenating" denotes the use of a hydrogenation method which results in the addition of H_2 to the group $-CH=CH-CH=CH-$ in Compound V to form the group

$-CH_2-CH=CH-CH_2-$ without affecting any other groups in the compound.

The process of the present invention may constitute part of a process for preparing oct-4-en-2,7-dione from sorbaldehyde as follows:



Accordingly the present invention also provides a process for preparing oct-4-en-2,7-dione which comprises ethynylating sorbaldehyde to form Compound I, subjecting Compound I to conditions for allylic rearrangement to form Compound II, then converting Compound II to Compound V by a process according to the present invention and then partially hydrogenating Compound V to form oct-4-en-2,7-dione, Compound I being defined herein.

The ethynylation of sorbaldehyde can be effected by first reacting acetylene and an amide of such basic metals as lithium, sodium, potassium and calcium to form an acetylide. The resulting acetylide can thereafter be condensed with sorbaldehyde to form a metal complex which can be readily hydrolyzed to Compound I by the addition of water, dilute acid, or ammonium salt solution. The metal amide can be added to the reaction mixture as such to react with the acetylene, or it can

be formed *in situ* by employing liquid ammonia as a solvent and adding the basic metal thereto. In forming the metal amide *in situ*, a trace amount (e.g. 10 mg.) of ferric nitrate is usually added to catalyze or accelerate the reaction, although such catalyst materials are not necessary to effect the reaction. Also, an acetylenic Grignard reagent having the formula $\text{CH}\equiv\text{CMgX}$, wherein X is a halogen atom, can be condensed with sorbaldehyde, the resulting complex being hydrolyzed in the manner described above to produce Compound I.

The ethynylation of sorbaldehyde by means of a metal acetylide, an acetylenic Grignard reagent, or with related reactants mentioned above, is effected in the usual manner with regard to reaction conditions. Sufficient acetylide or Grignard reagent or other reactant e.g. amide and acetylene is added to the reaction mixture to condense with substantially all of the sorbaldehyde, the presence of excess acetylide or Grignard reagent in the reaction mixture not deleteriously affecting the reaction.

The ethynylation step of the present invention may be effected in a solvent substantially inert to sorbaldehyde, the acetylide or the Grignard reactants or amide and acetylene and the product of the reaction. Suitable solvents include diethyl ether, toluene and benzene. As pointed out above, liquid ammonia can be used as the solvent when a metal acetylide is employed in the present process.

Temperatures ranging from about room temperature up to the reflux temperature of the solvent are more usually employed in the condensation reaction of sorbaldehyde and the acetylide or Grignard reagent. When liquid ammonia is employed as the solvent for the reaction, the temperature of the liquid ammonia is the reaction temperature.

The condensation reaction is effected until substantially all of the sorbaldehyde is reacted, with reaction times ranging from about $\frac{1}{2}$ hour to about 5 hours being typical reaction periods.

Compound I is thereafter subjected to an allylic rearrangement to form Compound II. An aqueous acid solution is preferably employed. Typical of such acids are sulphuric acid, hydrochloric acid, phosphoric acid, formic acid, acetic acid, trichloroacetic acid and comparable acidic materials. Aqueous solutions of acids in concentrations of from about 0.5% to about 20% acid can be suitably employed, a concentration of about 5% acid being a typical concentration. The present allylic rearrangement can be effected by merely associating, preferably with constant stirring or agitation, Compound I with the aqueous acid until substantially all of Compound I is rearranged to Compound II. Reaction times vary with such variants as the temperature,

concentration of the acid and the degree of stirring or agitation of the reactants. Reaction times usually range from about 1 hour to 15 hours, or even to 20 hours.

With extended reaction times, it is desirable to add a small amount of an antioxidant material such as hydroquinone, butylated hydroxy anisole, butylated hydroxy toluene, and related materials, to the reaction mixture, as well as to effect the reaction in an inert atmosphere such as nitrogen.

The rearrangement can be effected at room temperature although elevated temperatures up to reflux temperatures can be used to increase the rate of the reaction.

In the process of the present invention, Compound II can be treated by either of two closely related sequences of process steps to form Compound V. Compound II can be oxidized to form Compound III, which can thereafter be hydrated to form Compound V or alternatively Compound II can be hydrated to form Compound IV, which can thereafter be oxidized to form Compound V.

The oxidation of Compound II to Compound III and the oxidation of Compound IV to Compound V according to the present invention are preferably effected with a slurry of manganese dioxide in an organic solvent inert to the reactants and the resulting reaction products, such solvents as diethyl ether, acetone, methyl ethyl ketone, benzene, hexane and toluene being typical solvents suitable for the reaction. Likewise, the present oxidations can be effected with such oxidizing agents as tertiary butyl chromate or by an Oppenauer oxidation with an aluminium tertiary alkoxide in the presence of a hydrogen acceptor. A substantial excess of oxidizing agent is desirably employed to assure a substantially complete oxidation of the carbinol group of Compound II or Compound IV to a ketone group. With the preferred manganese dioxide oxidizing agent, the oxidation can be suitably effected at room temperature by merely stirring or associating the oxidizing agent with the carbinol compound to be oxidized, although temperatures up to the reflux temperature of the solvent employed can be used to increase the rate of the reaction. The oxidation is continued until the carbinol groups of Compound II and Compound IV are substantially completely oxidized to the ketone groups of Compound III and Compound V respectively. Typical reaction times range from about 1 hour to 24 hours, and more usually from about 10 hours to 20 hours.

In the present invention the acetylenic bonds in Compound II or in Compound III are hydrated with one molecule of water to form a ketone group in the respective compounds. Such hydrations can be effected with aqueous solutions containing hydration catalysts such as acidic materials like sulphuric acid, phosphoric acid and formic acid, in

combination with mercury compounds such as mercuric oxide and mercuric sulphate. Mixtures of about 0.5% to 10% by weight of acid in combination with about 20% to 50% by weight of mercury compound based on the weight of the acetylenic compound are more usually employed, although the amount of catalyst can be suitably varied even further, such variables as the particular catalyst, the solvent and the temperature of the reaction affecting the amount of catalyst that can be suitably used.

The reaction is more generally effected in an aqueous medium such as aqueous methanol, aqueous acetone or other aqueous solvent systems which are substantially inert to the reactants and the resulting reaction products. Likewise, the reaction can be effected in an aqueous medium containing a mercury compound and a major amount of an organic acid such as formic acid. The amount of mercury compound in such an aqueous organic acid medium is usually varied between about 1% and 10% by weight of the acetylenic compound. Likewise, such hydration catalysts as perchloric acid and boron fluoride can be utilized with or without mercury compounds in accordance with usual hydration practice.

The hydrations can be effected at room temperature although elevated temperatures up to the reflux temperature of the solvent are more generally employed to increase the rate of the reaction. The hydration reaction is allowed to proceed until substantially all of the acetylenic bond is hydrated to a ketone group. Reaction times usually range from about 15 minutes to about 5 hours, the time of reaction varying with the reaction temperature, the type and amount of hydration catalyst, the amount of stirring or agitation, and related reaction variables.

Compound V can be readily converted to Compound VI, by partial hydrogenation. Such a partial hydrogenation can be effected in an amine solvent, such as pyridine, containing metal-acid combinations which are capable of generating hydrogen. The combination of zinc dust and an acid such as acetic acid is a typical metal-acid combination which can be suitably employed. Compound V is hydrogenated under carefully controlled reaction conditions to minimize the complete hydrogenation of Compound V. Accordingly, the partial hydrogenation is preferably effected at depressed temperatures, such as from about 0°C. to room temperature. Reaction times usually vary from about 5 minutes to about 30 minutes.

No particular purification methods are needed to treat the intermediates formed in the processes of the present invention prior to subjecting them to subsequent steps in the synthesis. However, it is common practice to purify or "work-up" Compounds I, II, III and IV by distillation under vacuum, and

Compound V as well as the final product, Compound VI, by crystallization from organic solvents at depressed temperatures. Likewise, other well-known purification methods such as chromatography can be employed to "work-up" the intermediate products and the final product of the synthesis.

The preparations of Examples 1 and 2 illustrate the conversion of sorbaldehyde to oct-4-en-2,7-dione according to the invention employing the processes of the invention for converting Compound II to Compound V via Compound III and Compound IV respectively.

EXAMPLE 1

PREPARATION OF COMPOUND I

A 9 gram sample of lithium metal was added to 3 litres of liquid ammonia in a 3-necked round bottom flask cooled with a dry ice-acetone bath and fitted with a dry ice-acetone reflux condenser, mechanical stirrer, dropping funnel, and an acetylene inlet tube. A trace (about 10 mg.) of ferric nitrate was added and the mixture was stirred at about -50°C. until the resulting blue colour disappeared. Acetylene was passed into the resulting mixture under agitation for about 2 hours. Thereafter, 96.1 grams of sorbaldehyde were added dropwise over a period of 30 minutes. The resulting mixture was stirred for one hour, 80 grams of solid ammonium chloride slowly added, the resulting ammonia gas evaporated, and the reaction mixture extracted with an equal volume of diethyl ether. The ether solution was washed three times with one-quarter its volume of saturated ammonium chloride solution, three times similarly with saturated sodium chloride solution and thereafter dried over anhydrous sodium sulphate. The ether was removed by distillation *in vacuo* to give 122 grams of Compound I having $E_{1\text{cm}}^{1\%}(229\text{ m}\mu) = 2289$, representing a yield of 96%.

PREPARATION OF COMPOUND II FROM COMPOUND I

122 grams of Compound I prepared as described above and 610 cc. of 5% aqueous sulphuric acid containing about 0.1 gram of hydroquinone antioxidants were shaken for three hours in an inert nitrogen atmosphere at about 25°C. The reaction mixture was then neutralized with aqueous sodium bicarbonate and thereafter extracted with an equal volume of diethyl ether. The resulting ether extraction was washed three times with one-quarter its volume of saturated aqueous sodium chloride solution and then dried over anhydrous sodium sulphate. The ether was removed by distillation yielding 122 grams of Compound II having $E_{1\text{cm}}^{1\%}(259\text{ m}\mu) = 2326$, corresponding to a yield of 93.6%.

PREPARATION OF COMPOUND III FROM
COMPOUND II

A 100 gram portion of Compound II prepared as described above was dissolved in 1.4 litres of diethyl ether, and to this mixture was slowly added 1.2 kilograms of powdered manganese dioxide. The resulting mixture was allowed to stand for 16 hours at 25°C., and thereafter filtered, and the filter cake washed on the filter with about 500 cc. of diethyl ether. The ether was distilled from the resulting combined filtrates to yield 88.1 grams of Compound III having $E_{1\text{cm}}^{1\%} (290 \text{ m}\mu) = 2010$ \equiv a yield of 80%.

PREPARATION OF COMPOUND V FROM
COMPOUND III

To a solution of 100 grams of Compound III, prepared by the method described above, in 500 cc. of 85% aqueous methanol containing 1.34 grams of sulphuric acid, was added a mixture of 5 grams of mercuric oxide and 30 grams of mercuric sulphate. The resulting mixture was refluxed for 30 minutes, cooled, and extracted three times with one-quarter its volume of diethyl ether. The combined ether extracts were washed with one-quarter their volume of saturated aqueous sodium chloride solution, dried over anhydrous sodium sulphate and concentrated to a volume of approximately 200 cc. On cooling the resulting concentrate to -20°C., 64.3 grams of crystalline Compound V having $E_{1\text{cm}}^{1\%} (275 \text{ m}\mu) = 2435$ (\equiv a yield of 56%) resulted.

PREPARATION OF COMPOUND VI FROM
COMPOUND V

To a cooled (5°C) solution of 5 grams of Compound V prepared as described above in 50 cc. of pyridine containing 10 cc. of glacial acetic acid was added 5 grams of zinc dust. The temperature of the resulting mixture was allowed to rise to 25°C. over a period of about 10 minutes. This mixture was filtered, poured into 350 cc. of 2 N. sulphuric acid and extracted three times with 125 cc. portions of diethyl ether. The combined ether extracts were washed to neutrality with saturated aqueous sodium chloride portions, dried over anhydrous sodium sulphate and the ether removed by distillation under reduced pressure to yield 3.6 grams of oct-4-en-2,7-dione, having a melting point of 31-32°C. (\equiv a yield of 71%.)

EXAMPLE 2

Example 1 was repeated as far as the preparation of Compound III. Compound V was then prepared as follows:—

PREPARATION OF COMPOUND V FROM
COMPOUND III

To a solution of 5 grams of mercuric sulphate in 500 cc. of 85% aqueous formic acid was slowly added 100 grams of Compound III. The resulting mixture was stirred for 2

hours at room temperature and thereafter for 30 minutes at 50°C. After cooling to 25°C., the reaction mixture was diluted with about one-half its volume of diethyl ether and the resulting crystallized inorganic salts in the reaction mixture filtered off. The ether and the formic acid were then distilled off *in vacuo*, and the residue, after the addition of about 100 cc. of saturated aqueous sodium chloride solution, was extracted with an equal volume of chloroform. The chloroform extract was washed with an equal volume of saturated aqueous sodium bicarbonate solution and dried over anhydrous sodium sulphate. The chloroform was distilled off *in vacuo* and the resulting residue crystallized from twice its volume of diethyl ether to yield 66.5 grams of Compound V having $E_{1\text{cm}}^{1\%} (275 \text{ m}\mu) = 2435$ \equiv a yield of 58%.

Oct-4-en-2,7-dione was then prepared as described in Example 1.

EXAMPLE 3

Compound II was prepared as described in Example 1 and Compound IV was prepared therefrom as follows:—

PREPARATION OF COMPOUND IV FROM
COMPOUND II

To a 2.5 gram sample of Compound II was slowly added with agitation a cooled mixture (5°C.) containing 0.26 grams of mercuric oxide, 1.7 cc. of sulphuric acid, 10 cc. of water and 1.5 cc. of ethanol. The temperature of the reaction mixture was allowed to rise to 25°C. over a period of 1.75 hours with continuous stirring. The mixture was then diluted with 100 cc. of diethyl ether, filtered, and the resulting ether layer washed with one-quarter its volume of saturated aqueous sodium chloride solution. After drying the ether solution over anhydrous sodium sulphate, the ether was removed by distillation. A 2.5 gram residue having $E_{1\text{cm}}^{1\%} (270 \text{ m}\mu) = 1300$ resulted which contained approximately 50% of Compound IV.

Compound V was then prepared as follows:

PREPARATION OF COMPOUND V FROM
COMPOUND IV

To a 2 gram sample of Compound IV dissolved in 15 cc. of diethyl ether was added 15 grams of powdered manganese dioxide. The resulting reaction mixture was left at 25°C. for 18 hours, filtered, and the filter cake washed on the filter with 50 cc. of diethyl ether. The ether was removed from the resulting combined filtrates to yield 1.88 grams of Compound V having $E_{1\text{cm}}^{1\%} (274 \text{ m}\mu) = 861$ \equiv a yield of approximately 40%. Oct-4-en-2,7-dione was then prepared from Compound V by the method of Example 1.

The unsaturated diketone, oct-4-en-2,7-dione, is particularly valuable for use in the

synthesis of various carotenoids such as beta-carotene, lycopene and other related polyene hydrocarbons. The preparation of beta-carotene from oct-4-en-2,7-dione, is described in German patent No. 818,942.

5 The synthesis of oct-4-en-2,7-dione provided by the present invention has the advantages that the yields of the intermediates and final product are good and that it requires easily available starting materials and avoids the use of hazardous reagents such as lithium aluminium hydride.

WHAT WE CLAIM IS:—

15 1. A process for preparing Compound V which comprises oxidising Compound II to Compound III and then hydrating Compound III to form Compound V, or which comprises hydrating Compound II to form Compound IV and then oxidising Compound IV to Compound V, Compounds II, III, IV and V being defined herein.

2. A process according to claim 1 wherein a slurry of manganese dioxide in an inert solvent is used to oxidise Compound II to Compound III or to oxidise Compound IV to Compound V.

3. A process according to claim 2 in which the inert solvent is diethyl ether.

4. A process according to any of claims 1 to 3, wherein an aqueous acid medium containing a mercury compound is used to hydrate Compound II to form Compound IV or to hydrate Compound III to form Compound V.

5. A process according to claim 4 in which from 0.5% to 10% by weight of acid and from 20 to 50% by weight of mercury compound, based on the weight of Compound II or Compound III, is used.

6. A process according to claim 5 in which an aqueous methanol solution containing 1.3% of sulphuric acid, 30% of mercuric sulphate and 5% mercuric oxide, is used to form Compound V from Compound III, said percentages being by weight based on the weight of Compound III.

7. A process according to claim 5 in which aqueous formic acid containing 5% of mercuric sulphate is used to form Compound V from Compound III said percentage being by weight

based on the weight of Compound III.

8. A process for preparing oct-4-en-2,7-dione which comprises ethynylating sorbaldehyde to form Compound I, subjecting Compound I to conditions for allylic rearrangement to form Compound II, then converting Compound II to Compound V by a process according to any of claims 1 to 7 and then partially hydrogenating Compound V to form oct-4-en-2,7-dione, Compound I being defined herein.

9. A process according to claim 8 wherein the sorbaldehyde is ethynylated by condensing an alkali metal acetylide or an acetylenic Grignard reagent with the sorbaldehyde and hydrolysing the condensate to form Compound I.

10. A process according to claim 9 wherein lithium acetylide is formed in liquid ammonia to which the sorbaldehyde is then added to form the condensate.

11. A process according to any of claims 8 to 10 wherein Compound I is rearranged allylically to form Compound II by treating it with an aqueous acid solution containing from 0.5% to 20% of acid by weight.

12. A process according to any of claims 8 to 11 wherein Compound V is hydrogenated with glacial acetic acid and zinc dust to form the oct-4-en-2,7-dione.

13. A process for preparing Compound V which comprises oxidising Compound II to Compound III and hydrating Compound III to form Compound V or which comprises hydrating Compound II to form Compound IV and oxidising Compound IV to Compound V, Compounds II to V being defined herein, substantially as herein described.

14. Processes for preparing oct-4-en-2,7-dione according to claim 8 substantially as herein described.

15. Oct-3,5-dien-2,7-dione (Compound V as herein defined) whenever prepared by a process according to any of claims 1 to 7.

16. Oct-4-en-2,7-dione whenever prepared by a process according to any of claims 8 to 12 and 14.

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